REMARKS

A. Status of the Claims/Formalities

Claims 1-50 were filed with the original application, and claims 10, 12 and 21-50 have been canceled in response to a restriction requirement. Claims 1-9, 11, and 13-20 are presently pending in the application. Claims 1-8 and 13-18 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 1 and 8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Maziere *et al.* Claims 1-9, 11, 13, 15-16, and 19-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Maziere *et al.* and Park *et al.* in view of Pastey *et al.* Claim 14 stands rejected under §103(a) as being unpatentable over Maziere and Park *et al.* in view of Pastey *et al.* Claim 17 stands rejected under §103(a) as being unpatentable over Maziere and Park *et al.* in view of Pastey *et al.* and Fisher *et al.* Claim 18 stands rejected under §103(a) as being unpatentable over Maziere and Park *et al.* in view of Pastey *et al.* and Gruber *et al.* The specific grounds for rejection and applicants' response to them are set forth in detail below.

B. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-9, 11, and 13-20 are pending in the application and stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. The examiner once again argues that several phrases in the claims are indefinite.

Specifically, the examiner mentions the expression "a subject," in claim 1, as not being defined in the specification. Applicants submit that it is entirely unreasonable to read "a subject" as anything but an intact organism. There is no logical interpretation of this term that would

justify an argument that it reads on a cell. Thus, the rejection is improper and should be withdrawn. However, in the interest of advancing the prosecution, the term has been removed and replaced with "patient," which term is used throughout the specification, for example, at page 4, line 24.

Next, the examiner argues that the expression "severe combined immunodeficiency" in claim 4 is indefinite because "severe" is a relative term and the expression is not defined in the specification. The examiner cannot conduct prosecution in a vacuum. The term severe combined immunodeficiency defines a particular disease state that is well known to those of skill in the art. In fact, a "Google" search of this term resulted in over **25,000 hits**!!!!! There is even a website using the acronym for severe combined immunodeficiency – scid – at www.scid.net. Thus, it cannot seriously be argued that this term is indefinite.

The examiner also argues that the specification does not clearly define the phrase "an inhibitor of isoprenylation that is distinct from said HMG-CoA reductase inhibitor," and that the terms "a nucleoside analog composition" and "a protease inhibitor" in claims 15 and 16, respectively, are indefinite as not being defined in the specification. Applicants once again traverse. In order for claims to satisfy the definiteness standard, the inventor need only ensure that "one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993). Claims need only "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). Furthermore, "[t]he purpose of claims is not to explain technology or how it works, but to state the legal boundaries of the patent grant. A claim is not

'indefinite' simply because it is hard to understand when viewed without the benefit of the specification." *S3 Inc. v. nVIDIA Corp.*, 239 F.3d 1364, 59 U.S.P.Q.2d 1745 (Fed. Cir. 2001).

Section IV, page 17 is entitled "Inhibitors of Isoprenylation" which is clearly distinct from the previous section entitled "Inhibitors of HMG-CoA Reductase." Section IV contains a detailed description of geranylgeranyl transferase and farnesyl transferase inhibitors which are both clearly distinguishable from the previously described HMG-CoA reductase inhibitors. One skilled in the art would reasonably understand that "an inhibitor of isoprenylation that is distinct from said HMG-CoA reductase inhibitor," as read in light of the specification, refers to compounds such as geranylgeranyl transferase and farnesyl transferase inhibitors. The examiner has not even bothered to address this line of argument. As such, the record reflects that the burden remains with the examiner to establish indefiniteness.

Finally, with regard to the terms "nucleoside analog composition" and "protease inhibitor," applicants again emphasize that the definiteness standard is whether "one skilled in the art would understand the bounds of the claims." Both nucleoside analogs and protease inhibitors are well known drugs for treating viral infections such that one skilled in the art would know the meaning of those terms. See attached Exhibit A. Further, in U.S. Patent 6,573,247 (McGuigan *et al.*), the term "nucleoside analog" is used in the abstract, the claims, and the specification without detailed explanation. Evidence that one skilled in the art would know what is meant by the term "protease inhibitor" can be found in U.S. Patent 6,558,923 (Paulous *et al.*), where the terms "protease" and "protease inhibitor" are used numerous times in the abstract, claims, and specification without being expressly defined in the specification. The examiner's only response is to argue that each patent is examined on its own merit. ***This misses the point entirely!!!*** The point is that these ***issued patents*** do not bother to define these terms, so why

should the instant application, ***filed later than these other patents***, have to do so. Once again, the examiner has failed to shift the burden to applicants on this issue.

Accordingly, applicants respectfully request that the rejection of claims 1-9, 11 and 13-20 under 35 U.S.C. § 112, second paragraph be withdrawn.

C. **Rejection under 35 U.S.C. § 102(b)**

Claims 1 and 8 stand rejected under 35 U.S.C. §102(b) as being anticipated by Maziere *et al.* (Maziere). The examiner contends that Maziere discloses a method of inherently treating or inhibiting infection of a cell by a virus as described in claims 1 and 8. The examiner argues that because Maziere teaches that HMG-CoA reductase inhibitors are useful inhibiting HIV-1 expression in H9 human T lymphocytes they are useful in inhibiting the HIV cycle in patients. Applicants respectfully traverse, as claims 1 and 8 are not inherently nor expressly anticipated by Maziere.

As argued previously, anticipation requires that each and every element of the claimed invention be described, either expressly or inherently, in a single prior art reference. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1327, 58 U.S.P.Q.2d 1545, 1552 (Fed. Cir. 2001); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Applicants presently claim "[a] method of inhibiting infection of a cell by a virus in a subject comprising the step of administering to said ***subject*** an inhibitor of HMG-CoA reductase" where the virus can be the HIV virus as well other various types of viruses. Emphasis added. Since Maziere only teaches that the HMG-CoA reductase inhibitor, lovastatin, is capable of inhibiting HIV expression in the human H9 ***cell line***, it cannot anticipate use of HMG-Coa reductase inhibitor to prevent HIV infection of cells in a ***subject***, specifically *in vivo*.

The examiner's only rebuttal is to argue that "treatment of a subject" reads on *in vitro* methods. Applicants cannot fathom such an interpretation, but as stated above, the claims have been amended to change "subject" to "patient." Accordingly, claims 1 and 8 clearly are not anticipated by Maziere. Therefore, reconsideration and withdrawal of the rejection is requested.

D. Rejection Under 35 U.S.C. § 103(a) - Maziere & Park *et al.* in view of Pastey *et al.*

Claims 1-9, 11, 13, 15-16, and 19-20 stands rejected under §103(a) as being unpatentable over Maziere and Park *et al.* (Park) in view of Pastey *et al.* (Pastey). Maziere discloses the use of a HMG-Coa reductase inhibitors as a method of inhibiting HIV-1 expression in H9 human lymphocytes. Park teaches the use of HMG-Coa reductase inhibitors such as simvastatin and astrovastatin to inhibit the geranylgeranylation of RhoA GTPase. The examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the invention, in view of the knowledge disclosed in Pastey, to employ HMG-Coa reductase inhibitors in a method of inhibiting infection of a cell by a virus such as RSV in a human, non-human, or a livestock mammal. The examiner also contends that through the teachings of Park and Pastey, one of ordinary skill in the art would have reasonably expected that HMG-CoA reductase inhibitors would have a beneficial therapeutic effect in inhibiting infection of a cell by a virus such as RSV in a subject such as in a human, a non-human mammal, or a livestock animal. Finally, the examiner argues that one of ordinary skill in the art at the time of the invention was made would have been motivated to employ HMG-CoA reductase inhibitors in combination with a nucleoside analog composition in a method of inhibiting infection of a cell by a virus such as RSV in a human, non-human, or a livestock mammal. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if even one element is missing, a *prima facie* case of obviousness does not exist.

The first step in establishing a *prima facie* case of obviousness is presenting evidence that Maziere and Park, in view of Pastey, teach or suggest all of the claim limitations of applicants' present claims. Because none of the three references discloses a method of using HMG-CoA reductase inhibitors to inhibit infection of a cell by a virus in subject *in vivo*, they do not teach or suggest all of the claim limitations found in claim 1. Additionally, the examiner admits that the cited prior art "does not expressly disclose the employment of HMG-CoA reductase inhibitors in a method of inhibiting infection of a cell by a virus such as RSV in ***a human, a non-human mammal, or a livestock animal.***" As the claims have now been amended to recite "patient," there can be no argument that the claims read on *in vitro* methods. Therefore, Maziere, Park, and Pastey fail to establish a necessary element required for a *prima facie* case of obviousness.

Another element of a *prima facie* case of obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The examiner states that Pastey teaches "that RhoA-derived peptide inhibits RSV."

Applicants believe the examiner is referring to Pastey, Gower *et al.* (C33, PTO-1129 submitted June 11, 2002) rather than Pastey, Crowe *et al.* (C32, PTO-1129 submitted June 11, 2002). Regardless, Pastey, Gower *et al.* and Park are directed at solving two completely different problems. The purpose of Park's paper was to examine the effect of HMG-CoA reductase inhibitors on the cholesterol metabolic pathway. On the other hand, Pastey, Gower *et al.* examines the inhibition of RSV syncytium formation using peptides. Thus, these references have very little to do with each other.

Furthermore, in contrast to both Pastey, Gower *et al.* and Park, Maziere discloses an *in vitro* method of using HMG-CoA reductase inhibitors to inhibit ***HIV-1*** expression in a H9 cell line. As mentioned before, Park addresses the use of HMG-CoA reductase inhibitors for the upregulation of ***TGFβ***. Park does not teach that HMG-CoA reductase inhibition of RhoA geranylgeranylation inhibits viral expression. Therefore, Park has no relevance to the inhibition of RSV or HIV-1 expression. Moreover, Pastey, Gower *et al.* is strictly directed toward inhibition of RSV and parainfluenza virus type 3 (PIV-3) using peptides, not HMG-CoA reductase. The RhoA-derived peptide inhibition is based purely on a process of inhibiting virus attachment of cell-to-cell fusion, while the mechanism for lovastatin action was unstated or assumed to be related to membrane function. Furthermore, neither Park nor Pastey, Gower *et al.* make any mention of the HIV-1 virus. Thus, the examiner has attempted to make a circuitous connection between Maziere and Pastey, Gower *et al.* through Park. However, the approach fails since each reference deals with distinct issues that only peripherally bear up on the claimed invention. Based on the divergent teachings of these three references, a person of ordinary skill in the art would have no motivation to combine Maziere, Park and Pastey, Gower *et al.*

Additionally, the examiner argues that by combining the teachings of Maziere and Park in view of Pastey, Gower *et al.* one with ordinary skill in the art would be motivated to use a nucleoside analog such as AZT in combination with a HMG-CoA reductase inhibitor to inhibit infection of a virus such as RSV. The only reference that mentions a nucleoside analog is Maziere, which states "[m]ost of the drugs used ... such as AZT, are inhibitors of viral replication. However such compounds [appear] to be ***poorly effective*** ...." Emphasis added. One of ordinary skill in the art would understand Maziere not as teaching that a nucleoside analog should be used in combination with HMG-CoA reductase inhibitors, but rather that HMG-CoA reductase inhibitors should be used ***instead*** of nucleoside analogs. Neither Park nor Pastey, Gower *et al.* make any mention of nucleoside analogs. Thus, no motivation remotely exists for one skilled in the art to combine the teachings in the three references to combine a nucleoside analog and HMG-CoA reductase inhibitors.

In response to this line of argument, the examiner submits that applicants are attacking the references individually, which is not proper. This is false. Applicants have shown why the individual teachings of the references preclude their logical combination, in light of the understanding of those of skill in the art. One ***must*** examine the teachings of the references individually to understand why they are not readily combined as argued by the examiner. Applicants again submit that the examiner is stringing the references together in a tenuous fashion using applicants' claims as a "road map" to the invention. This is a classic example of "hindsight reconstruction" which is not permitted under the law. *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, where no prior art reference or references of record

convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.")

The third element required for a *prima facie* showing of obviousness is that in combining references, there be a reasonable expectation of success. Pastey, Crowe *et al.* discloses the discovery that RSV F that interacts with RhoA and facilitates RSV syncytium formation. Pastey, Gower *et al.* also discloses a ***peptide*** that spans the F binding domain of RhoA and inhibits RSV syncytium formation. However, Pastey, Gower *et al.* makes no mention of HMG-CoA reductase inhibitors. On the other hand, Park teaches that HMG-CoA reductase inhibitors are capable of inhibiting the ***geranylgeranylation*** of RhoA for the purpose of upregulating transforming growth factor-β (TGFβ), but fails to address peptides. The two references involve two completely distinct mechanisms. Most importantly, ***Park does not present any evidence that inhibition of RhoA geranylgeranylation also inhibits viral expression***. In fact, no mention is made at all whether inhibition of RhoA geranylgeranylation could be successful in inhibiting RSV expression, ***much less inhibition of HIV-1!*** Thus, no person skilled in the art would have a reasonable expectation of success by combining the teachings of Park and Pastey, Crowe *et al.*, in the context of Maziere's teachings.

The examiner has failed entirely to even address this aspect of applicants' previous response. A proper obviousness analysis requires that ***each*** element of a *prima facie* case be established, ***including likelihood of success***. Not only has the examiner advanced a reasonable argument in support of this factor, applicants now have provided clear reasons to believe that there is ***no*** basis for likelihood of success. In light of the final Office Action's silence on this point, applicants submit that the rejection is, and continues to be, improperly maintained.

Thus, because the examiner has failed to present a *prima facie* case of obviousness on all three elements, applicants respectfully request that the rejection of claims 1-9, 11, 13, 15-16, and 19-20 be withdrawn.

E. Rejection under 35 U.S.C. § 103(a) – Maziere & Park in view of Pastey

Claim 14 stands rejected under §103(a) as being unpatentable over Maziere and Park in view of Pastey. The examiner argues that Maziere and Park in view of Pastey teaches the combination of a HMG-CoA reductase inhibitor and an inhibitor of isoprenylation in inhibiting infection of a cell by a virus such as RSV. Applicants respectfully traverse.

Claim 14 is not obvious over Maziere and Park in view of Pastey for the reasons mentioned in section D, above. Moreover, applicants submit the following arguments against the examiner's contention of obviousness.

A *prima facie* case of obviousness requires that Maziere and Park in view of Pastey teach or suggest all of the claim limitations in claim 14. The examiner admits that the employment of HMG-CoA reductase inhibitors in combination with an inhibitor of isoprenylation that is distinct from said HMG-CoA reductase inhibitors in a method of inhibiting infection in a cell by a virus such as RSV is not expressly disclosed in the references. Claim 14 states "[t]he method of claim 1 ... administering to said ***patient*** an inhibitor of isoprenylation that is distinct from said HMG-CoA reductase inhibitor." As emphasized before, a patient is not a cell nor an *in vitro* method. Park only teaches the use of HMG-CoA reductase inhibitors and two inhibitors of isoprenylation ***in vitro***, and Maziere and Pastey are limited to *in vitro* applications as well. Clearly, all the claim limitations in claim 14 have not been suggested or taught by the references. Thus, the examiner has not established an element required for a *prima facie* case of obviousness.

A second element needed to establish a *prima facie* case of obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Maziere and Park in view of Pastey, Gower *et al.* Applicants disagree that any motivation exists to combine the teachings of Maziere and Park in view of Pastey, Gower *et al.* As discussed above, Park teaches the use of isoprenylation inhibitors for the purpose of studying the regulation of TGFβ signaling. Park never discusses inhibition of the RSV virus, nor does it teach that inhibitors of isoprenylation can be used to inhibit infection by any virus much less the RSV virus, much less any mention of HIV-1. Similarly, Maziere does not teach the use of inhibitors of isoprenylation to inhibit the RSV virus, thus potentially implicating Pastey, Gower *et al.* To the contrary, Maziere teaches the use of HMG-CoA reductase inhibitors to inhibit ***HIV-1***, and even then, to inhibit replication, not virus entry through a receptor. Even taking into account Pastey, Gower *et al.*, no evidence is presented in the prior art suggesting that HMG-CoA reductase inhibitors, with or without inhibitors of isoprenylation, should be used to inhibit infection by even the RSV virus. Based on the lack of evidence and the divergent teachings of Park and Maziere, a skilled artisan with knowledge generally available to one skilled in the art would not be motivated to combine these references. Therefore, a second requirement for a *prima facie* case of obviousness has not been met.

The examiner argues that legal precedent (*Kerkhoven*) supports the obviousness of "combin[ing] two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose." Unfortunately, the flaw with this argument is that HMG-CoA reductase inhibitors ***have not been shown to be useful for treating HIV infections in vivo.*** Thus, the rejection effectively collapses

into the same issue discussed above, and applicants again submit that there is no basis for finding obviousness here.

The final element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of Maziere and Park in view of Pastey would be successful. As mentioned above, Pastey, Gower *et al.* and Park disclose two completely different inhibition mechanisms for two completely different purposes – peptide inhibition of RSV, and HMG-CoA reductase inhibitors. Pastey, Gower *et al.* teaches the use of a peptide to bind to the F protein binding site of RhoA in inhibiting RSV syncytium formation. In contrast, Park teaches the inhibition of geranylgeranylation of RhoA in the upregulation of TGFβ signaling by use of inhibitors of isoprenylation. Inhibition of RSV syncytium formation ***through a RhoA derived peptide*** teaches nothing with regard to possible inhibition of RSV viral infection any other RhoA-related mechanisms. Park does not even mention that inhibition of geranylgeranylation of RhoA by HMG-CoA and isoprenylation inhibitors could inhibit any viral infection, much less RSV, and much, much less HIV-1. Moreover, Maziere does not teach geranylgeranylation in discussing the mechanism in which HMG-CoA reductase inhibitors prevents HIV-1 expression. Simply stated, no evidence exists that shows that inhibition of geranylgeranylation of RhoA by HMG-CoA and isoprenylation inhibitors reduces RSV or any viral expression. The examiner has produced no evidence that one skilled in the art would be reasonably successful in combining the divergent teachings of Maziere, Park, and Pastey. Thus, the prior art cannot be read as providing any reasonable likelihood of success. Accordingly, the examiner has failed to establish the final element necessary for a *prima facie* case of obviousness.

The examiner argues, in response, that there is no showing of unexpected results for the claimed combination. However, unexpected results are only required ***once the examiner has established a proper prima facie case of obviousness***. As should be evident, there is ***no such prima facie case***. Thus, it remains the examiner's burden to explain why *in vitro* studies in HIV-1, when combined with other *in vitro* studies using an entirely different composition result in a ***reasonable*** likelihood of success for treating a human infectious disease.

Based on the examiner's failure to establish all three of the required elements for a *prima facie* case of obviousness, the Applicants respectfully request that rejection of claim 14 be withdrawn.

F. Rejection under 35 U.S.C. § 103(a) - Maziere and Park in view of Pastey & Fisher *et al.*

Claim 17 stands rejected under §103(a) as being unpatentable over Maziere and Park in view of Pastey and Fisher *et al.* (Fisher). The examiner argues that Maziere and Park in view of Pastey and Fisher teaches the combination of a HMG-CoA reductase inhibitor and an antibody composition in inhibiting infection of a cell by a virus such as RSV. Applicants respectfully traverse.

As mentioned above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. If any one element is missing, a *prima facie* case of obviousness does not exist.

The first element necessary to establish a *prima facie* case of obviousness requires that Maziere and Park in view of Pastey, Gower *et al.* and Fisher teach or suggest all of the claim limitations in claim 17. The examiner admits that none of the references expressly disclose combining HMG-CoA reductase inhibitors with monoclonal or polyclonal antibodies. Fisher is the only reference that contains any discussion about antibodies and only discusses the use of antibodies alone in treating RSV. Fisher does not even discuss the possibility of combining antibodies with other therapies. Additionally, none of the four references teaches the use of HMG-CoA reductase inhibitor in combination with antibody therapies ***in vivo***. Although Fisher teaches administration of antibodies alone *in vivo*, Maziere, Park, and Pastey only discuss administration of HMG-CoA reductase inhibitors *in vitro*. Because Fisher along with Maziere, Park and Pastey, Gower *et al.* fail to suggest all the claim limitations, a *prima facie* case of obviousness has not been established.

Another element required that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Maziere and Park in view of Pastey, Gower *et al.* and Fisher. "The mere fact that references can be combined or modified does not render the resultant combination obvious ***unless the prior art also suggests the desirability of the combination***." *Manuel of Patent Examining Procedure* (MPEP) § 2143.01 (8th Ed. Rev.). Emphasis added. None of these references make any suggestion of combining antibodies and HMG-CoA reductase inhibitors to inhibit infection by a virus such as RSV. As noted above, the only reference which mentions antibodies is Fisher. which does not teach the use of any other treatment for RSV, only the use of

antibodies. Fisher also never suggests the use of antibodies in combination with HMG-CoA reductase inhibitors.

Therefore, the issue is whether one of ordinary skill in the art with knowledge that is generally available would be motivated to combine Maziere and Park in view of Pastey, Gower *et al.* and Fisher. Applicants disagree that one of ordinary skill in the art would be motivated to combine these references. Many therapies have been investigated in treating viral infections, but Fisher does not even mention the use of antibodies in conjunction with any of these therapies let alone use with HMG-CoA reductase inhibitors. There are hundreds of potential therapy combinations for inhibiting viral infections such that a skilled artisan could not possibly know that antibodies could be combined with other therapies if the prior art does not recommend any therapies to use or even suggest that the possibility of such a combination exists. Consequently, Maziere and Park in view of Pastey, Gower *et al.* and Fisher fail to establish an element necessary for a *prima facie* case of obviousness.

The examiner argues that legal precedent (*Kerkhoven*) supports the obviousness of "combin[ing] two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose." Unfortunately, the flaw with this argument is that HMG-CoA reductase inhibitors ***have not been shown to be useful for treating HIV infections in vivo.*** Thus, the rejection effectively collapses into the same issue discussed above, and applicants again submit that there is no basis for finding obviousness here.

The final element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of Maziere and Park in view of Pastey,

Gower *et al.* and Fisher would be successful. Applicants submit that there would be no reasonable expectation of success in combining HMG-CoA reductase inhibitors and antibody compositions in inhibiting infection of a cell by a virus such as RSV. The examiner again presents no evidence that combining HMG-CoA inhibitors and antibodies would reasonably result in success. The result of combining drug therapies is impossible to predict. Much experimentation must occur before a combination of viral therapies proves to be successful. The examiner appears to assume that combining HMG-CoA reductase inhibitors and antibodies will automatically result in successful inhibition of RSV expression. There simply is no basis for such an assumption. Furthermore, none of the four references provide any guidance or recommendations as to whether combining HMG-CoA reductase inhibitors and antibodies would be successful in inhibiting RSV infection. At best, the prior art presents an "obvious to try" situation. Specifically, the combination of HMG-CoA reductase inhibitors and an antibody composition may or may not be successful. However, the PTO's reviewing court has consistently held that "'obvious to try' is not the standard" and "does not render a claim obvious." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 U.S.P.Q.2d 1065 (Fed. Cir. 2000), *In re Roemer*, 258 F.3d 1303, 59 U.S.P.Q.2d 1537 (Fed. Cir. 2001). The Applicants stress that a reading of the prior art cannot in any way provide a ***reasonable*** likelihood of success. As such, Maziere and Park in view of Pastey and Fisher do not establish a reasonable expectation of success as required for a *prima facie* case of obviousness.

The examiner argues, in response, that there is no showing of unexpected results for the claimed combination. However, unexpected results are only required ***once the examiner has established a proper prima facie case of obviousness***. As should be evident, there is ***no such prima facie case***. Thus, it remains the examiner's burden to explain why *in vitro* studies in HIV-

1, when combined with other *in vitro* studies using an entirely different composition result in a ***reasonable*** likelihood of success for treating a human infectious disease.

The examiner has not provided evidence to establish that claim 17 was *prima facie* obvious at the time of filing. Accordingly, applicants respectfully request that the rejection of claim 17 be withdrawn.

G. Rejection under 35 U.S.C. § 103(a) - Maziere & Park in view of Pastey & Gruber *et al.*

Claim 18 stands rejected under §103(a) as being unpatentable over Maziere *et al.* (Maziere) and Park *et al.* (Park) in view of Pastey *et al.* (Pastey) and Gruber *et al.* (Gruber). The examiner argues that Maziere and Park in view of Pastey and Gruber teaches the combination of a HMG-CoA reductase inhibitor and ribavarin in inhibiting infection of a cell by a virus such as RSV. Applicants respectfully traverse.

In light of the reasons presented in Sections D, E and F, above, Applicants disagree that claim 18 is obvious over Maziere and Park in view of Pastey and Gruber. Furthermore, Applicants submit the following arguments against the examiner's assertion of obviousness.

One element necessary to establish a *prima facie* case of obviousness requires that Maziere and Park in view of Pastey and Gruber teach or suggest all of the claim limitations in claim 18. The examiner admits that none of the references expressly disclose combining HMG-CoA reductase inhibitors with ribavarin. Gruber is the only reference that contains any discussion about ribavarin and only discusses the use of ribavarin with human immunoglobin (IVIG) in treating RSV. Furthermore, none of the four references teaches the use of HMG-CoA reductase inhibitor in combination with ribavarin ***in vivo***. Although Gruber teaches

administration of ribavirin *in vivo*, Maziere, Park, and Pastey only discuss administration of HMG-CoA reductase inhibitors *in vitro*. Because Gruber along with Maziere, Park and Pastey fail to suggest all the claim limitations, a *prima facie* case of obviousness has not been established.

Another element required that is required in order for a *prima facie* case of obviousness to exist is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Maziere and Park in view of Pastey and Gruber. None of these references make any suggestion of combining ribavarin and HMG-CoA reductase inhibitors to inhibit infection by a virus such as RSV.

Therefore, the relevant inquiry is whether knowledge that is generally available to one of ordinary skill in the art would supply the motivation to combine Maziere and Park in view of Pastey and Gruber. Applicants submits that one skilled in the art would not be motivated to combine Maziere and Park in view of Pastey and Gruber. Gruber teaches the use of ribavirin in combination with IVIG or "another agent". However, Applicants reiterate that many therapies and agents are available in treating viral infections. Gruber provides no examples of "another agent" nor does it even mention HMG-CoA reductase inhibitor as such an agent. Although Gruber mentions that ribavirin may be used in combination with "another agent", the fact that it makes no suggestion of any particular combination of ribavirin and "another agent" besides IVIG does not provide any information to skilled artisans that would motivate them to specifically combine HMG-CoA reductase inhibitor with ribavirin. Additionally, one skilled in the art would not be motivated to specifically combine HMG-CoA reductase inhibitor with ribavirin to inhibit RSV when the divergent teachings of Maziere and Park in view of Pastey do

not disclose the use of HMG-CoA reductase inhibitor to inhibit infection by the RSV virus. As such, Maziere and Park in view of Pastey and Gruber fail to establish an element required for a *prima facie* case of obviousness.

The examiner argues that legal precedent (*Kerkhoven*) supports the obviousness of "combin[ing] two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose." Unfortunately, the flaw with this argument is that HMG-CoA reductase inhibitors ***have not been shown to be useful for treating HIV infections in vivo.*** Thus, the rejection effectively collapses into the same issue discussed above, and applicants again submit that there is no basis for finding obviousness here.

A third element in establishing a *prima facie* case of obviousness requires that there be a reasonable expectation that modifying the teachings of Maziere and Park in view of Pastey and Gruber would be successful. One skilled in the art would have no reasonable expectation of success by modifying the teachings of Maziere and Park in view of Pastey and Gruber. Gruber states a "[c]ombination of ribavirin with another agent ***might*** provide improved protection against RSV infection." Emphasis added. Although Gruber describes a successful combination of ribavarin and IVIG, it provides no evidence that a combination of ribavirin and "another agent" would provide the same results. Additionally, Gruber provides no guidance as to which combination of ribavirin and another agent besides IVIG would reasonably expected to be successful. The language, "might", in no way would assure a skilled artisan that combining ribavirin with any agent, let alone a HMG-CoA reductase inhibitor, would reasonably result in successful inhibition by RSV.

Additionally, the examiner argues that additive therapeutic effects would be reasonably expected. This simply is not the case. Combining viral therapies is a highly unpredictable art. Trial and error is often required to determine the proper combination of therapies. Evidence of such unpredictability is observed in Gruber. Gruber mentions that ribavirin and IVIG were tested *in vitro* to look for additive effects, but found that additive effects were ***minimal*** in inhibiting RSV. Gruber appears to show that the success in combining ribavirin and IVIG *in vivo* was ***unexpected*** in view of these *in vitro* results. Furthermore, it appears that some other *in vivo* interaction ***specific*** to IVIG and ribavirin is responsible for the additive effect as shown by the statement "[f]urther studies are indicated to determine how IVIG and ribavirin interact with local antibody and cellular elements to limit RSV infection." Clearly, the success in Gruber was not due to expected additive results, but as a result of unpredictable trial and error. Gruber gives no indication that similar success would come about from the combination of HMG-CoA indicators and ribavarin. As mentioned in section F above, the prior art, at most, describes an "obvious to try" situation which does not render a claim obvious. Accordingly, the examiner has not established an element necessary for a *prima facie* case of obviousness.

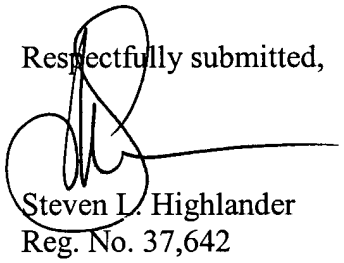
The examiner argues, in response, that there is no showing of unexpected results for the claimed combination. However, unexpected results are only required ***once the examiner has established a proper prima facie case of obviousness***. As should be evident, there is ***no such prima facie case***. Thus, it remains the examiner's burden to explain why *in vitro* studies in HIV-1, when combined with other *in vitro* studies using an entirely different composition result in a ***reasonable*** likelihood of success for treating a human infectious disease.

In view of the examiner's failure to satisfy any of the three elements needed for a *prima facie* case of obviousness, the Applicants respectfully request that the rejection to claim 18 be withdrawn.

H. Conclusion

Applicants submit that, in light of the foregoing, all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have and questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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